Remarks

Claims 22-25, 27-31, 33-34, and 36-38 are pending in the application. Claims 1-21, 26, 32, 35 and 39-47 have been cancelled without prejudice or disclaimer. The Applicants expressly reserve the right to prosecute the subject matter of these claims in a continuing or divisional application, as appropriate.

The specification has been amended as described below. No new matter has been added. The amendment to the specification includes a substitute specification and a marked-up version to show where the changes were made.

Objection to Trademark and its Use

The use of the trademark Polyheme® in the specification stands rejected because it is not capitalized and it is not accompanied by generic terminology. The Applicants have amended the specification to correct these errors. To implement this amendment, the Applicants have provided a Substitute Specification, including a marked up version to show where the changes were made. The specification now recites "POLYHEME® acellular red blood cell substitute" for all instances of the use of "Polyheme®."

Objection to the Specification and Claims

The specification and claims stand objected to because of what the Examiner perceives as an inconsistency in the use of the term "unit." The Examiner is concerned that that the prior art reference, Gould, *et al.,* refers to "one unit" as 50g, while the specification refers to one unit as 500 ml. *See* Gould, *et al.*, J. Trauma: Injury, Infection and Critical Care 43(2):325-332 (1997) and the specification at ¶¶ [0029], [0037], [0043] and [0051]. The Examiner is also concerned

with what is perceived as an internal inconsistency in the specification because "1000g" is used in conjunction with "10 L" (*see, e.g.,* ¶¶ [0043] and [0051] referring to "1000g, 10L").

Applicants respectfully submit that the specification is internally consistent, and is consistent with Gould, *et al.* In Gould, *et al.,* one unit of "Poly SFH-P" is described as 50 g human polymerized hemoglobin. *See* Abstract and p. 326. Gould, *et al.* also describes that this 50 g of hemoglobin is in 500 ml of solution. *See* p. 326, Table 1. Similarly, the specification teaches that one unit of polymerized hemoglobin solution has 50 g of polymerized hemoglobin in 500 ml of solution. *See, e.g.,* ¶¶ [0017], [0018], [0032, Table 2], [0034] and [0077]. Therefore, there is no inconsistency between Gould, *et al.* and the specification.

The instances where the specification refers to "(1000g, 10L)" are intended to refer to 1000 g of polymerized hemoglobin in 10 L of solution, which would be 20 units of the acellular red blood cell substitute. The text surrounding these instances makes that clear.

For the purposes of avoiding any further confusion, the Applicants have deleted from the specification all instances of "(1000g, 10L)" and the like. *See* ¶¶ [0033], [0037], [0043], [0050], [0051], and [0053]. Table 4 has also been amended to clarify that the hemoglobin solution is solution of 10% polymerized hemoglobin.

Accordingly, Applicants request that the objection to the specification and claims be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-3, 5-9, 11, 22, 23, 26-31, 33-37, 39-41, and 43-46 stand rejected under 35 U.S.C. § 102(b) as anticipated by Gould, *et al.* The Examiner finds that Gould, *et al.* teaches the

administration of a stroma-free polymerized hemoglobin solution at a rate of up to 6 L in 20 minutes. According to the Examiner, this disclosure anticipates the presently claim invention of treating patients for massive blood loss.

Claims 1-21, 26, 33, 35, 39-47 have been cancelled to expedite prosecution. Accordingly, the rejection with regard to these claims is moot. With regard to the remainder of the claims, Gould, *et al.* does not teach the a method of maintaining mean circulating Hb levels about 5.0 g/dL as presently recited in independent claim 22, or a method for treating a human having a hemoglobin concentration below 7 g/dL as presently recited in independent claim 30. Moreover, Gould, *et al.* does not teach the administration of a hemoglobin solution in an amount of at least one blood volume of a patient as recited in claim 22. The specification teaches that one blood volume in a 70kg man is about 5 L (*see* ¶ [0036]). With regard to claim 30, Gould, *et al.* does not teach the administration of the solution in an amount above 5 L sufficient to maintain arterial pressure above 60 mm Hg. While Gould, *et al.* teaches the infusion of up to 6 units (3 L, which is 40% less than one blood volume) of a polymerized hemoglobin solution to adult subjects, the claims are directed to the administration of at least 5 L, which is at least one blood volume of a patient, to maintain the appropriate circulating hemoglobin levels.

Accordingly, Gould, *et al.* does not anticipate the presently claimed invention because Gould, *et al.* does not teach all of the elements of the methods recited in independent claims 22 and 30. With regard to dependent claims 23, 27-31, 33-34, 36-38, each claim depends, either directly or indirectly, from claims 22 or 30, and contains all of the elements of claims 22 or 30. Therefore, Applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 102 with regard to claims 22 and 30 and each of the claims depending therefrom.

Rejections under 35 U.S.C. § 103

Claims 1-47 stand rejected under 35 U.S.C. § 103 as obvious over Gould, *et al.* taken with DeWoskin *et al.* (U.S. Patent No. 6,498,141) and Seghal, *et al.*, Surgery 95(4):433-438 (1984). The Examiner finds that Gould, *et al.* teaches the administration of up to six units of a polymerized hemoglobin solution in 20 minutes, depending upon the urgency of the situation. In addition, the Examiner finds that DeWoskin *et al.* teaches the administration of "up to at least about 5 L" of a polymerized hemoglobin solution. According to the Examiner, one of ordinary skill in the art would have been motivated to incorporate the administration of a large volume of hemoglobin solution as taught by DeWoskin *et al.* to patients who are suffering from massive hemorrhage as taught by Gould, *et al.* (*See* Office Action, p. 7). The Examiner also cites Sehgal, *et al.* as teaching the administration of a hemoglobin solution to patients through total exchange transfusion, resuscitation from normovolemic anemia, and resuscitation from hemorrhagic shock. (*Id.*, p. 9). According to the Examiner, this suggests that a polymerized hemoglobin solution can be applied to treat any kind of massive blood loss including anemia, ischemia and hypovolemic shock. (*Id.*).

Applicants respectfully disagree that the asserted combination of references renders the presently pending claims *prima facie* obvious. "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants have cancelled claims 1-22, 26, 32, 35 and 39-47 to expedite prosecution. Accordingly, the rejection with regard to those claims is moot. With regard to the remainder of the claims, Applicants respectfully disagree with the rejection because the Examiner has not established a *prima facie* case of obviousness. For example, the combination of Gould, *et al.*, DeWoskin *et al.* and Sehgal, *et al.* do not render the pending independent claims 22 and 30 *prima facie* obvious because this combination does not teach each and every element of these independent claims. As discussed above, Gould, *et al.* does not teach the a method of maintaining mean circulating Hb levels about 5.0 g/dL as presently recited in independent claim 22, or a method for treating a human having a hemoglobin concentration below 7 g/dL as presently recited in independent claim 30.

Likewise, DeWoskin *et al.* and Seghal, *et al.* do not teach each of the elements missing from Gould, *et al.* For instance, neither DeWoskin *et al.* nor Seghal, *et al.* teach a method for maintaining mean circulating Hb levels about 5.0 g/dL as presently recited in independent claim 22, or a method for treating a human having a hemoglobin concentration below 7 g/dL as presently recited in independent claim 30. While DeWoskin teaches the administration of "up to at least about 5L" of a polymerized hemoglobin solution and Seghal, *et al.* teaches the administration of 900 mL of 3-5% hemoglobin solution, these references do not suggest that the use of the hemoglobin solution for massive blood loss as presently claimed. Accordingly, the combination of references does not teach each and every element of independent claims 22 and 30.

In addition, the combination fails to render claims 22 and 30 *prima facie* obvious because the combination does not provide a reasonable expectation of success for the presently claimed invention. According to the Examiner, Seghal, *et al.* suggests the use of a polymerized

hemoglobin solution for treatment of any kind of massive blood loss, including anemia, ischemia and hypovolemic shock. Thus, the Examiner concludes that the combined teaching of the prior art renders *prima facie* obvious methods of administering polymerized hemoglobin solutions in an amount of at least 5 L wherein the administration maintains life-sustaining hemoglobin levels above 5 g/dL and arterial pressure above 60 mm Hg. (*See* Office Action, p. 9). What is missing from the Examiner's analysis is a showing that a skilled artisan, reading the cited references, would have a reasonable expectation of success in using a hemoglobin solution for treating patients with massive blood loss. Indeed, Sehgal, *et al.* teaches that the "clinically appropriate intravascular persistence for a red blood cell substitute is unclear" and "these data cannot be extended to the clinical setting." (p. 437, first column, second paragraph). This section of Seghal, *et al.* "suggest that poly SFH-P will be effective as an acelluar O_2 carrier, its efficacy will have to be confirmed ... ." (*Id.*) Indeed, Seghal, *et al.* identifies a number of issues that remain to be addressed including "nephrotoxicity, immunogenicity and the effect on the reticuloendothelial system." (*Id.*, top of second column). Thus, there is no suggestion here that the outcome of treating patients for massive blood loss with a full blood volume or 5 L of a hemoglobin solution would be successful. The Examiner's position seems to be that Seghal, *et al.* renders the presently claimed invention obvious to try, which is not the test for obviousness. But neither Seghal, *et al.* nor DeWoskin, *et al.* provide the skilled artisan with a reasonable expectation of success with the method of the claimed invention.

As an advance over the prior art, the Specification teaches significant and unexpected survival rates in patients suffering from massive blood loss when treated with a hemoglobin solution. Patients suffering from massive blood loss, and having red blood cell hemoglobin concentrations of less than 5.3 g/dL showed significant improvement in mortality than historical

controls. (*See* Specification, ¶ [0057] and Fig. 4). This includes patients having total red blood cell hemoglobin as low as 1 g/dL. (*Id.* ¶ [0054]). Nothing in the cited references suggest that this level of success of treating massive blood loss could be achieved with a polymerized hemoglobin solution.

Accordingly, the presently claimed invention of independent claims 22 and 30 is not rendered *prima facie* obvious by the asserted combination of Gould, *et al,* Seghal, *et al,* and DeWoskin, *et al.* The combination of these references does not teach or suggest each and every element of these claims, nor do the references provide a reasonable expectation of success of the presently claimed invention. Therefore, Applicants request that the rejection to these claims under 35 U.S.C. § 103 be withdrawn.

With regard to all of the remaining claims, each claim depends, either directly or indirectly, from claims 22 and 30. Therefore, those claims include all of the limitations of claims 22 and 30, and are not obvious for the same reasons that claims 22 and 30 are not obvious.

CONCLUSION

There may be other reasons for patentability for claims 22 and 30 and the dependent claims, and Applicants do not waive those arguments by failing to assert those arguments here. Applicants view the foregoing reasons as sufficient to establish that the claims are novel and nonobvious, but expressly reserve the right to make further argument regarding patentability of the claims.

With the above Amendments and Remarks, the Applicants respectfully submit that the application is now in a condition for allowance. If the Examiner is of the opinion that a

telephone conference would expedite prosecution of the application, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,
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